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Date of mailing (day/month/year) 21 April 1999 (21.04.99)	in its capacity as elected Office
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Applicant SHERMAN, Bernard, Charles	
1. The designated Office is hereby notified of its election made X In the demand filed with the International Preliminary 10 March 1999 In a notice effecting later election filed with the International Preliminary 2. The election X was was not was not was not was not Rule 32.2(b).	y Examining Authority on: 9 (10.03.99) national Bureau on:
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INTERNATIONAL APPLICATION PUBLISH	HED U	JNDER THE PATENT COOPERATION TREATY (PCT)
(51) International Patent Classification ⁶ : A61K 31/545, 9/14, 9/20	A1	(11) International Publication Number: WO 99/08683
Aur 30343, 7/14, 7/20		(43) International Publication Date: 25 February 1999 (25.02.99)
(21) International Application Number: PCT/CAS (22) International Filing Date: 7 August 1998 (Cost) (30) Priority Data: 2,209,868 15 August 1997 (15.08.97) (71)(72) Applicant and Inventor: SHERMAN, Bernard, [CA/CA]; 50 Old Colony Road, Willowdale, Onta 2K1 (CA).	07.08.9 C Charl	BY, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI,
(54) Title: PHARMACEUTICAL COMPOSITIONS COM	/IPRISI	NG CEFUROXIME AXETIL
(57) Abstract		

A co-precipitate of cefuroxime axetil and a water-soluble excipient. Process for making said co-precipitate, and pharmaceutical compositions for oral administration comprising said co-precipitate.

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PHARMACEUTICAL COMPOSITIONS COMPRISING CEFUROXIME AXETIL

BACKGROUND

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Cefuroxime axetil is an antibiotic effective against a wide spectrum of microorganisms. Antibiotics for oral administration should be in a form which provides high bioavailability, whereby absorption into the bloodstream from the gastro-intestinal tract is maximized.

For cefuroxime axetil, the prior art discloses substantial difficulties in making compositions for oral administration providing high bioavailability.

Pure cefuroxime axetil can be produced in crystalline form or amorphous form.

U.S. patent 4820833 discloses that the pure amorphous form is more soluble in water than the pure crystalline form and gives higher bioavailability upon oral administration.

U.S. patent 4897270 further discloses that film coated tablets comprising cefuroxime axetil (even in amorphous form) give low levels of absorption into the blood stream unless the tablets are formulated such that, when the tablet is ingested, the film coating ruptures very rapidly and the core then disintegrates immediately.

The prior art thus teaches that good absorption from tablets comprising cefuroxime axetil can be achieved only if the cefuroxime axetil used in the formulation is in pure amorphous form and the tablets contain sufficient disintegrant to cause them to disintegrate immediately in gastro-intestinal fluid.

It is the object of the present invention to overcome these limitations disclosed in the prior art.

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More specifically, one object of the present invention is to enable compositions of cefuroxime axetil for oral administration exhibiting high bioavailability without requiring use of cefuroxime axetil in pure amorphous form; and a second object of the present invention is to enable tablets for oral administration exhibiting high bioavailability without requiring that the tablets disintegrate immediately in gastro-intestinal fluid.

BRIEF SUMMARY OF THE INVENTION

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It has been found that the water solubility and hence bioavailability of cefuroxime axetil can be enhanced by making a co-precipitate comprising cefuroxime axetil and a water-soluble excipient.

15 It has further been found that tablets made from the co-precipitate exhibit satisfactory dissolution and bioavailability even if the tablets disintegrate over a period of many minutes, instead of immediately.

DETAILED DESCRIPTION OF THE INVENTION

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As aforesaid, it has been found that the water-solubility of cefuroxime axetil can be enhanced by making a co-precipitate of cefuroxime axetil with a water-soluble excipient.

The term "water-soluble excipient" will be understood to mean an ingredient having no therapeutic activity and being nontoxic (and thus suitable as an excipient) that has a solubility in water of at least 1 g per 1000 g at 20°C. The solubility will preferably be at least 1 g per 100 g at 20°C, and more preferably at least 1 g per 10 g at 20°C. Suitable water-soluble excipients will include, for example, povidone, polyethylene glycols, hydroxypropyl cellulose, methylcellulose, lactose, mannitol and sorbitol.

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A preferred water-soluble excipient is povidone. The amount of the water-soluble excipient used may be from about 2% to about 60% of the total weight of the co-precipitate, preferably from about 5% to about 25%, and most preferably about 10%.

The co-precipitate is made by dissolving pure crystalline cefuroxime axetil and the water-soluble excipient in a solvent or combination of solvents and evaporating the solvent or solvents. The solvent or solvents used will preferably be a solvent or solvents in which the cefuroxime axetil and the water soluble excipient have relatively high solubility so as to minimize the amount of solvent needed.

Since cefuroxime axetil has low solubility in water, it follows that a solvent other than water must be used to dissolve the cefuroxime axetil. Of the common organic solvents, the solvent in which cefuroxime axetil is most soluble is acetone. Acetone is thus a preferred solvent.

If the solvent selected to dissolve the cefuroxime axetil is also a good solvent for the water-soluble excipient, then only this one solvent is needed to dissolve both. However, if the solvent selected to dissolve the cefuroxime axetil is not a good solvent for the selected water-soluble excipient, then a second solvent is needed to dissolve the water-soluble excipient. That second solvent may be water or another organic solvent.

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If two solvents are used, they should be capable of being inter-dissolved to enable formation of a clear solution of the cefuroxime axetil and the watersoluble excipient in the combination of solvents.

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A solution of the cefuroxime axetil and water-soluble excipient in the solvent or solvents may be prepared either by dissolving the cefuroxime axetil and water-soluble excipient into solvents separately and then mixing the two solutions together, or by directly adding the cefuroxime axetil and water-soluble excipient to the solvent or mixture of solvents and mixing until a clear solution is formed.

After the solution of the cefuroxime axetil and water-soluble excipient in the solvent or solvents is prepared, it is necessary to then remove the solvent or solvents to obtain a dry co-precipitate.

This may be done, for example, by evaporating the solvent or solvents in a spray drying or roller drying process, or by evaporating the solvent or solvents under vacuum.

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The dried co-precipitate comprising cefuroxime axetil and the water-soluble excipient will then be further processed into a tablet.

This may be done by mixing the co-precipitate with other excipients and then processing the mixed powder into tablets on a tablet press. The other excipients will preferably include both a disintegrant and a lubricant.

The disintegrant is an ingredient which absorbs water and swells to cause the tablet to disintegrate when the tablet is immersed in gastro-intestinal fluid. Preferred disintegrants are water-insoluble cross-linked polymers, including, for example, croscarmellose sodium, sodium starch glycolate, and crospovidone.

A lubricant is needed to prevent sticking of the powder to the tooling in the tableting process. Preferred lubricants are stearic acid and metallic stearates, such as magnesium stearate.

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It will be understood that, as an alternative to preparing the dry co-precipitate by evaporation of solvents and then mixing the co-precipitate with other excipients in a subsequent step, the two steps may be done together. This may be done, for example, by spraying the solution of cefuroxime axetil and the water-soluble excipient onto other excipients in a fluidized bed drying system.

The invention will be further illustrated by the following examples, which are intended to be illustrative but not limiting of the scope of the invention.

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EXAMPLE 1

2000 g of acetone and 200 g of methanol were placed in a beaker. While stirring, 500 g of pure crystalline cefuroxime axetil was slowly added, and stirring was continued for about 5 minutes, until the cefuroxime axetil was fully dissolved. Stirring was continued and 50 g of hydroxy propyl cellulose was then added. Stirring was continued for another several minutes, until the hydroxy propyl cellulose was fully dissolved. The solution was then spray-dried to obtain a co-precipitate comprising 1 part hydroxpropyl cellulose to 10 parts cefuroxime axetil.

EXAMPLE 2

The following were mixed together:

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1	Total	-	180.0 g
-	colloidal silicon dioxide	-	<u>0.8 g</u>
	magnesium stearate	-	1.0 g
	croscarmellose sodium	-	44.0 g
	co-precipitate from example 1	-	134.2 g

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The mixed powder was compacted into slugs on a tablet press. The slugs were then ground into granules, and the granules were recompressed on a tablet press into tablets of weight 900 mg.

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In view of the proportions of ingredients as aforesaid, each tablet contained 671 mg of co-precipitate, which in turn contained 610 mg of cefuroxime axetil, which in turn is equivalent to about 500 mg of cefuroxime.

The tablets were tested for disintegration time using the method set out in the United States Pharmacopoeia, 23rd edition, page 1791. The disintegration time was over 30 minutes.

The tablets were also tested for dissolution as set out in the United States:

Pharmacopoeia, 23rd edition, page 316. The result was about 65% in 20 minutes and 90% in 60 minutes.

The dissolution specifications for cefuroxime axetil tablets on the said page 316 are 65% in 20 minutes and 80% in 60 minutes. The tablets of this example were thus found to comply with this specification, despite the relatively slow disintegration.

The dissolution specifications in the United States Pharmacopoeia are designed to ensure that tablets meeting the specifications will exhibit acceptable bioavailability.

EXAMPLE 3

2000 g of acetone and 200 g of methanol were placed in a beaker. While stirring, 500 g of pure crystalline cefuroxime axetil was slowly added, and stirring was continued for about 5 minutes, until the cefuroxime axetil was fully dissolved. Stirring was continued and 50 g of povidone was then added. Stirring

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was continued for another several minutes, until the povidone was fully dissolved. The solution was then spray-dried to obtain a co-precipitate comprising 1 part povidone to 10 parts cefuroxime axetil.

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EXAMPLE 4

The following were mixed together:

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	Total	-	177.4 g
	colloidal silicon dioxide	-	0.8 g
	magnesium stearate	-	1.0 g
	croscarmellose sodium	-	43.6 g
10	co-precipitate from example 3	-	132.0 g

The mixed powder was compacted into slugs on a tablet press. The slugs were then ground into granules, and the granules were recompressed on a tablet press into tablets of weight 900 mg.

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Again, in view of the proportions of ingredients as aforesaid, each tablet contained 670 mg of co-precipitate, which in turn contained 609 mg of cefuroxime axetil, which in turn is equivalent to about 500 mg of cefuroxime.

- The tablets were tested for disintegration time using the method set out in the United States Pharmacopoeia, 23rd edition, page 1791. The disintegration time was about 10 minutes.
- The tablets were also tested for dissolution as set out in the United States

 Pharmacopoeia, 23rd edition, page 316. The result was over 80% in 20 minutes
 and over 90% in 60 minutes.

The tablets of this example thus exhibited dissolution substantially faster than required by the United States Pharmacopoeia, again despite the fact that disintegration was not immediate.

What is claimed is:

- A co-precipitate comprising cefuroxime axetil and a water-soluble
 excipient.
 - 2. A co-precipitate as in claim 1 comprising from about 40% to about 98% by weight cefuroxime axetil and from about 2% to about 60% by weight water- soluble excipient.

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- 3. A co-precipitate as in claim 1 comprising from about 75% to about 95% by weight cefuroxime axetil and from about 5% to about 25% by weight water-soluble excipient.
- A co-precipitate as in claim 1 comprising about 90% by weight cefuroxime axetil and about 10% by weight water-soluble excipient.
- A co-precipitate as in any of claims 1 to 4 wherein the water-soluble excipient is selected from the group consisting of povidone, hydroxy
 propyl cellulose, methycellulose, lactose, mannitol and sorbitol.
 - 6. A process of production of a co-precipitate of any of claims 1 to 5 which comprises:-
 - dissolving the cefuroxime axetil and water-soluble excipient in a solvent or a mixture of solvents; and
 - evaporating the solvent or solvents.
 - 7. A process as in claim 6 wherein acetone is used as solvent.
- 30 8. A process as in claim 6 wherein the solvent or solvents are evaporated by spray-drying.

- A pharmaceutical tablet comprising a co-precipitate according to any of claims 1 to 5.
- 5 10. A pharmaceutical tablet as in claim 9 further comprising a disintegrant.
 - 11. A pharmaceutical tablet as in claim 10 wherein the disintegrant is a water-insoluble cross-linked polymer.
- 10 12. A pharmaceutical tablet as in claim 10 wherein the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate and crospovidone.
 - 13. A pharmaceutical tablet as in claim 10 further comprising a lubricant.
 - 14. A pharmaceutical tablet as in claim 13 wherein the lubricant is stearic acid or a metallic stearate.

nal Application No

PCT/CA 98/00773 A. CLASSIFICATION OF SUBJECT MATTER IPC 6 A61K31/545 A61k A61K9/14 A61K9/20 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 6 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category ^a 1 - 14EP 0 757 991 A (ACS DOBFAR S.P.A., MILAN Α (IT)) 12 February 1997 see the whole document 1 - 14FR 2 549 837 A (GLAXO) 1 February 1985 Α see the whole document 1 - 14EP 0 107 276 A (GLAXO) 2 May 1984 Α cited in the application see claims see page 23, line 1 - line 32 1 - 14GB 2 181 052 A (GLAXO) 15 April 1987 Α cited in the application see the whole document 1 - 14GB 2 204 792 A (GLAXO) 23 November 1988 Α see the whole document Patent family members are listed in annex. Further documents are listed in the continuation of box C. Χ Special categories of cited documents: "T" later document published after the international filing date or priority date and not in conflict with the application but "A" document defining the general state of the art which is not considered to be of particular relevance cited to understand the principle or theory underlying the invention earlier document but published on or after the international "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to "L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified) involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such docu-"O" document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled in the art. other means document published prior to the international filling date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of theinternational search Date of mailing of the international search report 25/11/1998 19 November 1998 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.

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According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 $\label{lem:minimum documentation searched (classification system followed by classification symbols)} IPC \ 6 \ A61K$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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Further documents are listed in the continuation of box C.	X Patent family members are listed in annex.
 Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publicationdate of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent tamily
Date of the actual completion of theinternational search 19 November 1998	Date of mailing of the international search report 25/11/1998
Name and mailing address of the ISA European Patem Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+31-70) 340-3016	Authorized officer Scarponi, U

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(PCT Article 36 and Rule 70)

PCT-1034		t's file reference	FOR FURTHER ACTION	See Notificat	tion of Transmittal of International Examination Report (Form PCT/IPEA/416)
nternational		•	International filing date (day/month/y	year)	Priority date (day/month/year) 15/08/1997
PCT/CA9			07/08/1998		15/06/1997
		it Classification (IPC) or na	ational classification and IPC		
A61K31/5	45				
Applicant					
SHERMA	N, B	ernard, Charles			
1. This ir and is	nterna trans	tional preliminary exam mitted to the applicant	nination report has been prepared according to Article 36.	by this Inter	rnational Preliminary Examining Authori
2. This F	REPO	RT consists of a total of	f 4 sheets, including this cover sh	ieet.	
h	oon a	mended and are the ba	ed by ANNEXES, i.e. sheets of the asis for this report and/or sheets co 507 of the Administrative Instructio	ontaining red	n, claims and/or drawings which have ctifications made before this Authority e PCT).
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3. This r	anort	contains indications rel	lating to the following items:		
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1	\boxtimes	Basis of the report			
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		4 1 Palaca - 4 - 4		entive step	and industrial applicability
III			opinion with regard to novelty, inv		
III IV		Lack of unity of invent	tion		
		Lack of unity of invent Reasoned statement of citations and explanat	tion under Article 35(2) with regard to I tions suporting such statement		entive step or industrial applicability;
IV	Ø	Lack of unity of invent Reasoned statement of citations and explanat Certain documents ci	tion under Article 35(2) with regard to I tions suporting such statement ited		
V	Ø	Lack of unity of invent Reasoned statement of citations and explanat Certain documents of Certain defects in the	tion under Article 35(2) with regard to i tions suporting such statement ited international application		
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Fax: (+49-89) 2399-4465

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00773

E.	Basis	of the	report
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1. This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

	the r	eport since they do	not contain a	mendmei	nts.):
	Desc	cription, pages:			
	1-8	;	as originally fil	led	
	Clai	ms, No.:			
	1-14	ı	as originally fi	led	
2.	The	amendments have	resulted in the	e cancella	ation of:
		the description,	pages:		·
		the claims,	Nos.:		
		the drawings,	sheets:		
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٧	. Rea	asoned statement blicability; citation	under Article s and explan	35(2) wi ations su	ith regard to novelty, inventive step or industrial upporting such statement
1	. Sta	tement			
	No	velty (N)	Yes: No:	Claims Claims	1-14
	lnv	entive step (IS)	Yes: No:	Claims Claims	1-14
	Ind	lustrial applicability	(IA) Yes: No:	Claims Claims	1-14

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA98/00773

2. Citations and explanations

see separate sheet

1. Section V

1.1 Cited Documents

The following documents (D) are referred to in this communication:

- D1: EP-A-0 757 991 (ACS DOBFAR S.P.A., MILAN (IT)) 12 February 1997
- D2: FR-A-2 549 837 (GLAXO) 1 February 1985
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- D8: EP-A-0 821 965 (BASF) 4 February 1998

1.2 Art 33(2) PCT (Novelty)

The present application meets the requirements of Article 33(2) PCT, because the subject-matter of claims 1-14 is new.

The subject-matter of independent claim is new because the previous art documents D1-D8 do not disclose any co-precipitate of cefuroxime axetil and a water-soluble excipient. The co-precipitate being new, also the process for making it and compositions containing it are new.

1.3 Art 33(3) PCT (Inventive step)

The present application does meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-14 does involve an inventive step.

The technical problem which the present application sought to solve vis-à-vis any of the prior art documents D1-D8 is "how to find an alternative bioavailable formulation of cefuroxime axetil". The solution proposed, i.e. the co-precipitation of cefuroxime axetil with a water-soluble excipient, cannot be derived from such documents by the person skilled in the art without the exercise of inventive abilities and therefore it involves an inventive step.

PCT



INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER See N (Form	lotification of Transmittal of In PCT/ISA/220) as well as, w	nternationalSearch Report here applicable, item 5 below.
PCT-1034 International application No.	International filing date (day/mor	th/year) (Earliest) Prior	rity Date (day/month/year)
PCT/CA 98/00773	07/08/1998		15/08/1997
Applicant		<u> </u>	
SHERMAN, Bernard, Charles	<u> </u>		
This International Search Report has bee according to Article 18. A copy is being tra	n prepared by this International Se ansmitted to the International Burea	arching Authority and is trans	smitted to the applicant
This International Search Report consists X It is also accompanied by a cop	of a total of 3sl y of each priorart document cited i	neets. n this report.	
Certain claims were found un	searchable(see Box I).		
2. Unity of invention is lacking(s	see Box II).		•
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	d with the international application.	•	
furn	nished by the applicant separately f	rom the international applicat	ion,
	but not accompanied by a sta matter going beyond the disc	tement to the effect that it dis osure in the international app	d not include dication as filed.
Tra	nscribed by this Authority		
4. With regard to the title, X the	text is approved as submitted by the	ne applicant	
	text has been established by this A		
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5. With regard to the abstract,	text is approved as submitted by the	ne applicant	
the Box	text has been established, accordictly. The applicant may, within one arch Report, submit comments to the	ng to Rule 38.2(b), by this Au month from the date of mailin	thority as it appears in g of this International
6. The figure of the drawings to be pub	linkad with the electront ic		
l —	suggested by the applicant.		None of the figures.
	cause the applicant failed to sugges	at a figure	
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INTERNATIONAL SEARCH REPORT

onal Application No

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A. CLASSI IPC 6	FICATION OF SUBJECT MATTER A61K31/545 A61K9/14 A61K9/20)	
According to	o International Patent Classification (IPC) or to both national classifica	tion and IPC	-
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IPC 6	ocumentation searched (classification system followed by classification A61K	n symbols)	
Documental	lion searched other than minimumdocumentation to the extent that su	uch documents are included in the fields	s searched
Electronic d	ata base consulted during the international search (name of data bas	se and, where practical, search terms u	sed)
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
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X Furth	ner documents are listed in the continuation of box C.	χ Patent family members are list	ed in annex.
° Special ca	tegories of cited documents :		
	ent defining the general state of the art which is not ered to be of particular relevance	"T" later document published after the or priority date and not in conflict cited to understand the principle of invention	with the application but
"E" earlier o	document but published on or after the international late	"X" document of particular relevance; t	
"L" docume which	nt which may throw doubts on priority claim(s) or	cannot be considered novel or cal involve an inventive step when the "Y" document of particular relevance; t cannot be considered to involve a	e document is taken alone he claimed invention
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	ent published prior to the international filing date but an the priority date claimed	"&" document member of the same par	ent family
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1:	9 November 1998	25/11/1998	
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	Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U	

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			ĪĒ	57726		24-03-1993
			JP	1892249		26-12-1994
			JP	6013526		23-02-1994
			JP	60075484		27-04-1985
			ŇĹ	8402372		18-02-1985
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			SE	8403897		30-01-1985
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		•	CH	657134		15-08-1986
			CZ	280528		14-02-1996
			CS	8305687		15-03-1988
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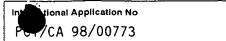
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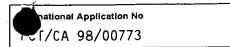
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